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Metabolism in health and metabolism in disease are two diverse problems which demand our closest study. Both are controlled by that biochemistry which is rapidly becoming the pathology of the future. The vital processes which are constantly occurring in the tissues and fluids of the body are deeply influenced by these chemical changes and by the toxic products that create a perversion of physiologic function. We have long known that bacteria were dangerous and destructive, but it has remained for chemical pathology to show us that the toxins which they engender are even more pathogenic. The influence of these chemical biproducts on the ocular structures is manifested chiefly as a localized hyperleucocytosis, of a toxic character, which falls, therefore, under the generic classification of chemotaxis. As this chemotactic process bears such an important relation to our subject I shall take the liberty

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of quoting the views of Da Costa[1] on this interesting problem:

"The exact manner in which pathologic leucocytosis arises is a question about which many conflicting views are held by different authorities, but the general trend of opinion at the present time attributes the increase chiefly to the influence of chemotaxis. According to the chemotactic theory of leucocytosis, the presence in the blood of certain chemical substances, produced by infective principles, is capable of exerting both an attractive and a repellent influence upon the ameboid leucocytes. If the collection of cells are attracted by such substances, the phenomenon is known as *positive chemotaxis,* but if, on the other hand, they are repelled, the condition is termed *negative chemotaxis.* This massing and repulsion of the leucocytes may be caused by various agents—by thermal and mechanical irritants, by bits of necrotic tissue which have gained entrance to the circulation, and especially by the presence in the blood of bacteria or of their metabolic products."

The perverted metabolism of the system, in so far as the eyes are concerned, is influenced by many complex factors. The endogenous causes are most prominent. Disturbed physiologic function is directly responsible for much of the pathogenesis. Lymphatic stasis, lymphatic insufficiency, and perverted lymphatic secretion are extremely important elements. Suboxidation and changed function due to disturbances of the ductless glands are powerful factors in this problem. Autointoxication arising from indigestion and constipation plays a prominent role. La grippe, the exanthemata, and in fact all febrile disturbances, are accompanied by an overproduction of perverted secretions that may prove chemically irritating to the delicate tissues of the eye, and thus produce optic neuritis or paresis of the extraocular muscles. Diseases of the liver or kidney are especially liable to cause a precipitation of toxins that may prove injurious to the eye. Of a similar character are the perversions arising during pregnancy and the fugacious disturbances of menstruation. Excessive emotional disturbances, such as fear, grief, anger or other unusual excitement, may cause a perversion of metabolism by interfering with the internal secretions and by lowering the systemic oxidation. Post-operative mania is a good example of such a perversion. Similar effects may be produced by sex-

ual excesses, by the nervous strain incident to exhausting mental application, by worry, by severe pain and by shock. High blood pressure often becomes a potent factor in originating localized lesions of the eye.

The ectogenous causes of disturbed metabolism arise chiefly from the ingestion of foods and drugs that are chemically irritating. Certain individuals may exhibit an idiosyncrasy against these, as for example such foods as strawberries, lobsters and mushrooms, or such drugs as atropin, quinin or morphin. Knies[2] believes that a pronounced toxemia may result from ptomains and toxalbumin when shellfish are eaten, even though no evidence of decomposition is present. He asserts that certain of these toxic products of malassimilation have a specific effect upon the eye; muscarin and neurin producing accommodative spasm and myosis, while tyrotoxin causes paralysis of accommodation and mydriasis. Of similar selective character are the toxic amblyopias following the ingestion of lead, quinin, methyl alcohol, tobacco and coffee. When these are taken in small quantities their corrosive action on the neuro-retinal fibers is insidious and partial, but when larger amounts are consumed the destruction may become sudden and complete. While alcoholic excesses have an ectogenous origin, their ultimate manifestations of perverted secretion and subkatabolism chiefly resemble those of endogenous toxins.

In addition to these there are many extraneous physical factors that bear an intimate relation to the etiology of these disturbances; exposure to extremes of heat and cold, high relative humidity, low barometric pressure, persistent east winds, drafts on the body or directly on the eye, deficiency of ozone in the atmosphere, inhalation of air containing an excess of carbon dioxide and disturbed electrical conditions, all of which tend to upset the metabolism.

The human organism is, therefore, a vast physico-chemical laboratory in which the most delicate and complex chemical reactions are constantly taking place; and this greater laboratory, as it were, includes many lesser laboratories which though more or less sequestrated and of minor importance, are nevertheless actively at work. The eye is the best organ of the body for the careful study of these manifestations because it is an end-organ, and because its pathologic processes are more open to inspection. All of the ocular structures may

be affected by these metabolic disturbances; the uveal tract most frequently, the retina and optic nerve less often, the cornea and sclera infrequently, and the muscular apparatus occasionally.

As we approach the question of what is the chief physiologic factor in perverted metabolism we are constrained to answer, suboxidation. When the oxidizing power of the blood is normal, when the ductless glands are actively furnishing their quota of internal secretion to stimulate this function, when the individual is in full possession of unimpeded respiratory powers, and when the air which he breathes is pure, there is no pabulum on which to breed disease. But when the oxygen intake is limited by respiratory obstruction, when the air is drawn from poorly ventilated rooms, and when the habits are sedentary, then every grain of coffee becomes a drachm of xanthin poison, every ounce of food becomes a pound of toxic proteid and every germ of disease becomes a giant of destruction.

The origin of suboxidation is of so complex a character that it is somewhat difficult to outline its various ramifications. Respiratory obstruction is probably the most important etiologic factor; it matters not whether this lies in enlarged tonsils, in adenoid vegetations, in hypertrophied turbinates or in the intranasal congestions that accompany mouth breathing. They are all foes worthy of our steel. But while we are studying these problems the collateral problems of perverted secretions in the nose and accessory sinuses, of disturbed digestion, and of intestinal toxemia are forced upon us as a part of the pathogenic whole that requires our most careful consideration.

Nothing can illustrate the relation of suboxidation to the perverted metabolism of ocular disease more characteristically than the clinical picture of corneal ulcer in the child, which is familiar to us all. The local ulcer is the smallest part of the symptom-complex. It is the sequel rather than the cause. Aside from the lacrimation, photophobia and blepharospasm there is but little evidence that the eye is involved. On the other hand, the nasal obstruction is pronounced. The secretions exuding from the nose are viscid, acrid and chemically irritating, often hanging down on the lip and causing eczematous excoriation. The nasal mucosa is so sensitive that a slight draft on the body or the raising of an eyelid will cause

a reflex fit of sneezing. The general symptoms, moreover, show the most typical effects of lowered oxidation. The skin of the whole body is ashy-pale, relaxed and leaky, being bathed in perspiration, while the hair is matted together by the great excess of moisture transuding from the scalp. In winter the perspiration and body chilling encourage overdressing or "bundling up," which only adds to the extreme sensitiveness already present.

The error of suboxidation in these cases can be best corrected by the restoration of free nasal breathing through local applications to the nose, and the withdrawal from the diet of those articles which demand a large amount of oxygen for their assimilation, such as tea, coffee, cakes and candy, coffee being the worst offender because of its high xanthin content, while the carbohydrates are a close second. When this has been accomplished the ocular lesion will promptly heal without further treatment.

Enlargement of the tonsils has been referred to as a pathogenic factor in suboxidation and its sequelæ. So far as we know the tonsil has but little internal secretion that might become perverted. Occasionally it accepts and transmits some infectious process. As a rule, however, the chief disturbing factor lies in its obstruction to breathing. The exact etiologic relation to the resultant lesion cannot always be explained. I can recall an anomalous case of marked papilledema in a child, that was persistent for over a year. During that period it was examined by many competent surgeons[3]. The condition was suggestive of brain tumor, but there were no focal symptoms. The most careful examination revealed absolutely no systemic lesion except enlarged tonsils. It was difficult to believe that edema of the nervehead could arise from respiratory obstruction. The presence of a certain degree of mental hebetude, however, recalled to my mind a series of mental defectives that were treated by the late Dr. Pepper, who believed that this subnormal mentality was the result of suboxidation, and proved it by having them relieved by tonsillectomy. The tonsils in my case were accordingly removed, following which the mental dullness cleared up and the edema of the optic nervehead promptly subsided. This case fortunately occurred several years ago. Today we would probably plan to relieve such a condition by a decompressive operation.

This observation of tonsillar interference with systemic oxidation was amply confirmed in a study I made last year of *"Symmetrical Lymphomata of the Lacrimal and Salivary Glands,"*[4] otherwise known as Mikulicz's disease. The etiologic question at issue was whether this chronic, non-inflammatory, glandular hypertrophy was incited by suboxidation associated with toxemia, or whether it was the result of a bacterial invasion. I shall quote what I then said in regard to the etiology of this rare condition because it is germane to several phases of our subject:

"The etiologic factors which most writers have recorded in these cases are: 1. Infection from buccal or conjunctival bacteria; 2, glandular irritation from some toxic agent in the blood or lymph stream causing lymphatic hyperplasia; and 3, some idiopathic origin. No specific bacteria have been demonstrated in these cases, the microscope usually revealing lymph cell infiltration of the interstitial tissue, which Mikulicz considers wholly responsible for the enlargement of the gland. Although bacterial infection is usually accompanied by an acute inflammatory process, no inflammation has been noted in these cases. Granting the possibility of infection, whence would it originate—from the eye, the mouth, or the nose? It has been stated that trachoma of the fornix has caused lacrimal adenitis (Baquis).[5] By analogy it is deduced that buccal bacteria might be transmitted through Steno's duct and thus infect the parotid (Hanau)[6]. I think it is much more probable, however, that the source of this invasion is nasal, and the means of transmission through the lymphatic capillaries. It certainly seems possible that a steady stream of toxic, bacteria laden secretions could be absorbed from the accessory sinuses (chiefly antrum) and carried directly to these contiguous glands. If, however, the origin is an infection from neighboring parts, why should the course of this disease be so sluggish and the condition remain unchanged for months and even years? *On the other hand, may this not be a chronic hyperleucocytosis strictly localized to these enlarged lymph glands?*

How can we explain the retrogression of these glandular swellings during the course of an acute intercurrent disease, and their recrudescence in some cases soon after convalescence? Kümmel[7] has reported such an occurrence during pneumonia,

Mikulicz[8] during appendicitis, Haeckel[9] through a severe enteritis, Delens[10] after an attack of cholera, Zirm[11] during an attack of erysipelas which followed partial excision of the gland, Quincke[12] from a similar cause, and Osler[13] after an attack of acute pleurisy with effusion. The query naturally arises, *does the general disease create a systemic polymorphonuclear leucocytosis that temporarily overwhelms and obliterates the localized hyperleucocytosis in the affected glands?*

There still remains for our consideration the view that some agent or chemical irritant in the lymph stream might cause an occlusion of the efferent lymph channel of the gland, and thus encourage leucocytic engorgement. This could occur in one of two ways: 1, from some perversion of glandular function resulting in the secretion of irritating materials and their retention within the gland substance, and 2, from irritation of the gland by some toxic fluid which is absorbed and transmitted from neighboring parts. Both of these processes may be properly included under the general term of chemotaxis or toxic leucocytosis.

The first proposition has a typical exemplification in the case McHardy[14] has placed on record, in which sudden enlargement of the lacrimal glands resulted from excessive indulgence in grief. Lagrange[15] has reported a case of temporary enlargement of these glands due to the perverted metabolism of the menstrual period. We also know that the antrum may secrete a fluid so irritating that it will cause swelling of the Schneiderian membrane and excoriation of the nostril and lip.

The second proposition is amply demonstrated, as I have previously intimated, by the fact that the fluid contents of the accessory sinuses (chiefly antrum) may be absorbed by the lymphatic capillaries and carried to these contiguous glands. In confirmation of this view I can recall having seen a case of chronic, indurated lymph node of the cheek that had been diagnosed sarcoma by several competent surgeons. It promptly and spontaneously disappeared after a nasal operation that restored antral drainage and free breathing. Whether this lymphoid hyperplasia was caused by a bacterial infection or by the absorption of an irritating lymph fluid was difficult to determine. That it was not sarcoma was convincingly demonstrated by its rapid and complete resolution."

In the two cases of lymphomata that my study was based upon resolution of the enlarged glands was promptly gained by tonsillar excision without medication, thus removing the respiratory obstruction and improving the systemic oxidation. In a subsequent case, however, great improvement was secured by the exhibition of thyroid extract in small doses. Arsenic, in the form of Fowler's solution, has usually been employed in these cases on account of its well known power of increasing the oxidation of the blood. These therapeutic facts tend, therefore, to confirm the view expressed as to the etiology of this disease.

Our problem, however, is not always solved so simply. I have already referred to the fact that several etiologic factors are frequently commingled and sometimes confused. Suboxidation may be supplemented by intestinal toxemia from constipation and digestive disorders, and both complicated by perverted sinus secretions that are at once infectious and toxic. Such a case was kindly referred to me in consultation about two years ago, by Dr. A. J. Bedell, of Albany.

His sight had been failing for about five years. During the preceding two years it had been reduced to 20/70 in the right eye and 20/50 in the left eye. The nervehead was somewhat pale, and the vitreous was made hazy by a cobweb opacity, the result of a former hyalitis. There were several isolated areas of old chorioiditis with pigmented deposits along the course of the vessels. The fields were contracted in both eyes, with central scotomata. He suffered from severe headaches for five years, but these had ceased about two years before. They were followed, however, by sharp attacks of facial neuralgia, chiefly in the spring and fall. He had enormous puffing of the septum and turbinates, causing mouth breathing at night. There was a slight escape of glairy mucopus from the antrum. A microscopic examination of the antral secretion revealed pneumococci in large numbers with a few streptococci. His vision would drop sharply whenever his breathing was obstructed by a cold in the head. The same blurring would occur whenever his bowels became constipated. The vision, however, recovered promptly as soon as these functions were restored to their normal condition. The vacillating vision showed that the infection or toxemia was intermittent and dependent upon the degree of autointoxication

and associated suboxidation. It did not, however, clearly demonstrate which factor was most pronounced. In fact, there was a possibility of both elements being active. He had previously been placed under a careful and systematic course of alterative treatment, but the results were disappointing.

The indications were in favor of intranasal cauterization in order to restore the ventilation and drainage of the nose. Following this operation his convalescence was rapid. His distant vision recovered from 20/70 to 20/30, the reading vision improved from J 10 to J 3, and the fields increased greatly on the temporal side.

Autointoxication from the intestinal tract is probably the form of metabolic disturbance that presents the greatest amount of clinical evidence. The subject has been ably discussed within recent years by de Schweinitz[16], who is convinced that uveitis, blepharitis, keratitis and certain neuro-retinal lesions result from the absorption of toxic substances that have been previously eliminated in the waste of the intestinal canal and have there undergone putrefactive decomposition. Woods[17] in a later communication freely endorses these views and cites some interesting cases in confirmation. Turck[18] has demonstrated that intestinal toxins, injected into the dog's circulation, will cause blindness through organic changes in the nervehead.

Unfortunately the urine in these cases of autotoxemia does not always show a relative elimination of tangible toxins, just as there is a lack of such evidence in serious ptomain poisoning. Jaffé,[19] however, is convinced that the degree of bacterial decomposition in the intestines can be measured by the amount of indican found in the urine. Elschnig[20] and Groyer[21] likewise accept the view that the presence of indican in the urine is pathognomonic of intestinal toxemia. De Schweinitz, on the other hand, believes that indican, while not always present, is very suggestive when it does appear. Although this interdependence seems probable, there is no evidence to show whether the indicanuria results from overproduction of intestinal toxins, or whether it is caused by their excessive absorption. On this point Hertz[22] pertinently remarks: "When excess of these substances is present in the urine of constipated individuals, it may just as well be due to the increase in the quantity absorbed, owing to the longer stay of the feces in

the colon, as to an increase in the quantity produced." While the presence of indican in the urine is significant of intestinal toxemia it should be remembered that indican is not in itself a toxic substance, but has probably been modified in the process of elimination.

Daland[23] endorses the view that indicanuria is significant of putrefactive absorption but believes that autointoxication may originate in the mouth and nasal sinuses as well as in the intestines, that indicanuria may be present without symptoms of toxemia and that constipation may exist without indicanuria. He further says: "Indicanuria has been observed in diarrhea, in association with indigestion, gastritis, enteritis, colitis, ulceration or obstruction of the small or large intestines, cholera, dysentery, Addison's disease, typhoid fever and inanition. Clinically, indicanuria occurs more readily when the hepatic function is disturbed than when this organ is normal."

Eales[24], of Birmingham, was one of the first to call attention to the fact that prolonged constipation was liable to cause recurrent intraocular hemorrhage. He believed that this was most prevalent in young men at about the age of puberty and was probably due to some unexplained vaso-motor spasm in the splanchnic region, which created a high arterial tension and thus caused a retinal or ciliary hemorrhage. I have treated and reported a number of these cases of hemorrhage from the ciliary body occurring in females[25] and in all of them there was abundant evidence of a toxemia aside from the acknowledged intestinal torpor. The fact that they cleared up under prolonged catharsis would seem to indicate that some irritating chemical was being absorbed from the intestinal tract and carried by the circulation to the minute end-vessels of the eye, where further escape was impossible and a minute rupture of the vascular sheath was the necessary result of the corrosive action and subsequent endarteritis. A similar toxic action from a disturbed renal function may be the origin of the so-called albuminuric retinitis and subretinal hemorrhages which occur in Bright's disease, although the disturbed suprarenal secretion probably participates in this lesion. The perverted metabolism of the menstrual period may also cause an intraocular hemorrhage, which is usually classified under the head of vicarious menstruation. I have observed several cases of this character.

Knies[26] expresses similar views as to the chemopathic origin of retinal hemorrhage in his discussion of Hirschberg's[27] cases. He says, "In very acute sepsis from the absorption of a large amount of the chemical products of decomposition, and toward the end of life, in the more chronic infections, extensive retinal hemorrhages are often found." The sudden hem-

Figure 1. Hemophilic extravasation into conjunctiva and cheek of right side. The facial scar was caused by a previous effort to excise redundant tissue after a similar attack seven years before.

orrhagic infiltrations occurring as sequelæ of la grippe probably have a similar origin.

In 1901 I had under my care an unusual case of hemophilic extravasation (Fig. 1) following chronic constipation, in which there occurred a tremendous cellular infiltration of the right cheek, accompanied by a vascular growth that projected from the conjunctiva of the right eye. The con-

dition so nearly resembled sarcoma of the antrum that a general surgeon advised immediate excision of the upper jaw. As I had previously treated her she was again referred to me for further study. I recalled that I had seen her in a similar attack some years before and that her history showed a recurrence of this disturbance every seven years. Prior to this last attack she had suffered severely from hyperidrosis, starchy indigestion and chronic constipation, the stools occurring at intervals of more than a week. The urinary examination was negative. The blood count showed erythrocytes, 4,820,000; leucocytes, 10,400; hemoglobin, 80 per cent. She was placed on thyroid extract and suprarenal extract, with a liberal use of cathartics. There was some improvement but it was slow. As she had marked nasal obstruction, which was increased by the pressure of the extravasation, it was finally decided to cauterize the inferior turbinate and the septal puff. One month later, simultaneous with the opening of the nostril, the resumption of free breathing caused prompt and complete absorption of the hemic infiltrate and, coincidently, the clearing up of a facial acne that had been present for more than a year.

Here again is shown a similarity in the disturbance of metabolism produced by constipation and by nasal obstruction, which can be traced back to the common ground of suboxidation. In other words, if the toxins are properly oxidized they are eliminated as harmless compounds. When they become so excessive that they cannot be oxidized they disturb the metabolism. This was further illustrated by this same patient who noticed that her tendency to hemorrhage from the ocular and buccal mucosa was suddenly increased when she indulged in strawberries or peaches. Another patient in the same class suffered from severe intraocular hemorrhage[28] after eating a box of strawberries. It has been shown that the acid in the strawberry may cause eruptions, hives, whorls, petechiæ, vomiting and attacks of nervousness in patients whose weak metabolic balance predisposes them to such disturbances. The chemical analysis of strawberries shows no especially irritating element, unless silicic acid (6.05 per cent.) may be so considered. It is claimed that silex is a deoxidizing agent and so might have a disturbing action on the oxygen content of the body fluids, somewhat analogous to that of the xanthin compounds and the carbohydrates previously referred to.

The modern view that the internal secretions furnished by the ductless glands are vital to the metabolic processes has been confirmed beyond cavil. A most instructive review of this subject has recently been made by Meltzer.[29] The influence of the thyroid gland on metabolism and particularly on the oxidizing power of the blood is of the highest importance. The action of thyroid extract as an alterative and an absorber of deposits led me many years ago to use it in ocular disease and especially for absorbing subretinal effusions and hemorrhages into the vitreous. It proved to be of marked value in the series of intraocular hemorrhages which I have previously mentioned. Administered in small doses (gr. j-ij, t.i.d.) it has frequently caused the prompt disappearance of a stagnant hemic deposit that had previously resisted a prolonged course of the iodides. Its restraining influence on hemophilic tendencies is well known. I have also found it of great value in reducing high arterial tension. Radcliffe[30] has recently shown the beneficial effects of thyroid extract in modifying the nutrition of the eye in cases of interstitial keratitis, while Risley[31] has confirmed this observation and demonstrated its additional value in the keratomalacia of certain cretinoid types.

As previously mentioned, lymphatic dyscrasiæ are pronounced pathogenic factors in the metabolic problem. Perverted lymphatic secretion is certain to follow the irritation of toxins when the reserve oxygen is low. This condition is particularly noticeable in interstitial keratitis, in serous iritis and in chronic glaucoma, where it often amounts to lymphatic stasis. The source of chemical irritation may occasionally be wholly localized within the eye. I have several times observed cataractous lenses that contained irritating chemicals and have seen these cause glaucomatous attacks and flannel-red eyes whenever a little of the retained lens substance escaped from the collapsed capsular cyst into the anterior chamber.

The query naturally arises, how can we control this condition of lymphatic stasis? In other words, is it possible to inhibit perverted lymphatic secretions and to stimulate fresh ones? I have found that this can undoubtedly be accomplished in the eye by administering hyoscin and morphin hypodermically to inhibit the flow of irritating lymph and by supplementing this with pilocarpin guarded by strychnin to stimulate the

secretion of fresh, active lymph. This observation seems to be a contradiction of the well known fact that in glaucoma we should administer eserin to contract the pupil and, *per contra,* that hyoscin is dangerous because it dilates the pupil. This dictum is undoubtedly true when hyoscin is instilled locally, but when administered internally it acts on the whole lymphatic system to inhibit the flow of perverted lymph and to cause its absorption before a mydriatic effect can be exerted upon the eye. Following this, the pilocarpin will stimulate the secretion of fresh lymph and thus relieve the local stasis. As soon as this stasis is removed the eserin already in the eye becomes active and the pupil immediately contracts.

My first experience in the use of this contradictory medication occurred in 1888. A patient suffering from severe glaucoma was suddenly plunged into acute mania. The pupils had remained widely dilated in spite of the prolonged use of a strong solution of eserin. I gave a hypodermic injection of hyoscin hydrobromate to control the maniacal excitement. On examining the eyes an hour later I found that the pupils had yielded to the eserin that had been previously instilled and were absolutely myotic. One week later I administered hyoscin to another case of glaucoma to relieve nocturnal neuralgia with equally good effects. The hyoscin was given internally for several nights with the result that the glaucomatous attack was completely relieved. A recent examination of this patient showed that there had been no return of the disease for more than twenty years. Since that time I have always used this combination to abort attacks of fulminating glaucoma and to control the exacerbations of this disease that are liable to occur.

It is equally valuable as an abortifacient in many similar conditions, and should prove useful in many phases of general disease. It will control post-operative mania if given in the early stages. It should only be used as an emergency remedy and should not be administered as a continuous medication. If the inhibitory effect is most desired the hyoscin and morphin may be given first, followed in a half hour by the pilocarpin and strychnin. If the lymphagogue action is indicated this sequence should be reversed, the pilocarpin and strychnin being given first, and the hyoscin and morphin later. In a few cases I have tried a dosimetric

effect by dividing a single dose of the alkaloids into six equal parts and giving one of these portions at more frequent intervals. As a rule, however, I administer the four drugs together, once or twice a day, for two or three days, either by the mouth or hypodermically, in the following dosage:

R.	Hyoscin. hydrobromat.	gr. 1/100
	Morphin. sulphat.	gr. 1/6
	Pilocarpin. nitrat.	gr. 1/8
	Strychnin. nitrat.	gr. 1/30

Similar lymphostatic effects may be secured by the use of any of the solonaceæ or their derivatives. The belladonna preparations are not, however, as efficient as those of hyoscyamus. Passiflora incarnata probably belongs to this group as it possesses a decidedly inhibitory action on perverted secretions. Its efficiency is especially noticeable in the later toxemias of pertussis, the exanthemata, la grippe and alcoholism. Picrotoxin (gr. 1/100) also exerts a somewhat similar effect. It has been used chiefly to check the night sweats of phthisis. I have often given it in ocular disease where a leaky skin denoted the dermic elimination of perverted secretions, the formation of which may often be prevented by its use. Morphin, while possessing a pronounced inhibitory action on secretions, has certain derivatives, such as dionin and apomorphin, that are active lymphagogues, although not so efficient as pilocarpin. The prolonged administration of morphin, like that of alcohol, creates perverted secretions similar to the endogenous toxins, which can only be counteracted by the use of hyoscin and pilocarpin.

The brilliant work of Ehrlich in the field of chemopathology has brought us a step nearer to the goal of chemotherapy. Chemopathy, or the chemical theory of disease, has thereby received an impetus that has focused the attention of medical investigators the world over. If the cultivation of this fascinating field of research shall abolish the present tendency to "medical nihilism" and forever banish that fatal dictum "not to give any drug that might mask the symptoms," a great and humane good will be accomplished and "rational therapeutics" will again assume the important position in medicine that it should naturally command.

Chemotherapy should have at least three objects in view:

(1) sterilization of the body fluids, in order to inhibit bacterial life without danger to the human organism, (2) neutralization of the irritating toxins and perverted secretions already circulating in the system, and (3) stimulation of fresh secretions from the lymphatic and ductless glands. The specific action of Ehrlich's arsenobenzol on the spirocheta of syphilis, seems to partially meet these indications; it acts as a direct lethal poison on the parasite istelf (spirillicide), it produces a radical change in the biochemistry of the body fluids, and in addition to this it seems to exert a pronounced stimulating effect on metabolism and nutrition that cannot be wholly explained through destruction of the spirocheta. In a case of interstitial keratitis (hereditary) recently treated for me through the courtesy of Dr. Judson Daland, the Wasserman reaction was strongly positive (+ 4). An intragluteal injection of gram. 0.5 was followed by slight ocular improvement. As the Wasserman reaction remained uninfluenced at the end of a month a second injection of gram. 0.3 was given intravenously. This was promptly followed by marked improvement. It is probable that this direct method of administration will prove the most efficient, although it will always require a skilled operator to execute the more elaborate technic.

The preparations of arsenic have long held sway as important therapeutic agents in metabolic disorders. Fowler's solution in combination with tincture of chloride of iron and mercuric chloride is an old established reconstructive tonic. Cacodylate of soda (gr. 1/20), digitalin (gr. 1/10) and thyroid extract (gr. ij) is a combination that has proved to be valuable in improving assimilation, and in reducing high blood pressure. Small doses of arsenious acid combined with the glycerophosphates will exert a direct influence on ocular disease through improvement of the general metabolism. Clemens' solution of the arsenite of bromine (m. iij-x) has demonstrated its value in diabetes mellitus. It has been my custom to resort to this chemotherapy in all ocular complications of this disease and to administer it for several weeks prior to any operative procedure. In two recent cases of cataract extraction this treatment had been carried out for about two years, until all diabetic symptoms had disappeared. The operations were wholly free from accident or post-operative reaction.

Donovan's solution of the iodides of arsenic and mercury

(m. v-xxx) is probably the most efficient combination of these drugs that we possess. While its specific action is best exhibited in the secondary and tertiary lesions of syphilis, its value as an alterative and an absorptive of plastic exudates in non-luetic cases is of the highest order. I have sometimes used it hypodermically to secure a prompt and decided action. Lugol's solution seems to exert a specific iodin therapy on the thyroid gland in exophthalmic goitre.

In tertiary lesions the large quantities of potassium iodide that have often been employed are suggestive of a chemical saturation of the body fluids. On the other hand, the lymphagogue action of the mecurials may be manifested when the dosage is extremely minute, the action being exerted directly on the eye as well as on the liver and if carried to excess resulting in stimulation of the salivary glands to the point of salivation. These small doses of calomel will stimulate the liver to destroy the intestinal toxins and thus correct the indicanuria. Phosphate of soda has a similar action on the liver and on the alimentary tract.

The massive doses of the salicylates which Gifford employs in sympathetic ophthalmitis also possess a chemical significance worthy of our closest study. According to the strength of the solution, salicylic acid when applied externally has a mildly corrosive or cleansing effect, as in ichthyosis, or an escharotic effect, as shown in the application of Ewing's solution to neoplastic growths. Whether a similar chemical action is manifested *in vitro,* or whether there is simply a sterilization with neutralization of certain toxic substances in the body fluids remains for the biochemist of the future to determine. The abortive action of salol and phenacetin in the early toxemia of la grippe or the dengue-like symptoms of a cold is probably the result of a similar chemical manifestation.

Although not as well known, the administration of carbolic acid, in what may be considered large doses, has a somewhat similar action to that of salicylic acid and the salicylates, to which it bears a close chemical relation. Contrary to the present belief, its administration will increase the urine and cause it to clear up and become a limpid or straw colored fluid. At the same time it stimulates a rapid improvement in the local lesion and a general physical betterment that is apparent to physician and patient alike. It is only when its poisonous action is pro-

nounced that a smoky urine develops, but this is manifested much more slowly when the body fluids are saturated with the toxic biproducts of perverted metabolism. A trial of this therapy in sympathetic inflammation has met with sufficient success to warrant the placing of other lesions under this therapeutic test. I am convinced that carbolic acid merits our further study from the new standpoint of chemotherapy.

A most instructive case of neuro-retinal edema with temporary blindness, successfully treated by this method, occurred in the practice of Dr. Herbert Fisher[32] of this city, a few years ago. The patient was suffering from post-puerperal nephritis and was apparently moribund from uremic coma when first seen. The urinary examination showed a test tube almost solid with albumen. Carbolic acid was administered, well diluted, every three hours, beginning with one minim in two ounces of water and increasing by one minim at each dose until ten minims of the acid and twenty ounces of water were given at once. This dosage was then continued three times a day for a week, at which time the patient was practically convalescent. In about two weeks she was able to be removed to the mountains where her health and vision were soon recovered and have been satisfactorily maintained for the past four years.

In another case of long continued, low grade septicemia, the result of a prostatic bruise, complicated by a small localized abscess, the same treatment was instituted, the phenol being increased as the patient acquired tolerance until symptoms of dizziness were manifested. The sensation of perineal weight soon disappeared and was followed by a feeling of stimulation and physical wellbeing that continued until complete recovery was assured.

A similar therapy was advocated by the late Dr. D. F. Woods,[33] of this city, about twelve years ago, in a severe case of tetanus with convulsions. He administered thirty minims of a 10 per cent solution of carbolic acid hypodermically every half hour the first day, every two hours the second day and every three hours the third, at which time the spasms began to lessen. The injections were then continued three times a day for about two weeks longer until the muscular rigidity had disappeared. There was profuse secretion of urine in which the odor of phenol was noticeable. Although slight

smokiness of the urine made its appearance on the second day, no other toxic symptoms developed. Whether the action of carbolic acid is wholly a sterilizing one, or whether it neutralizes certain toxic substances in the body fluids and ultimately encourages oxidation, are problems that remain to be solved. It should at least be kept in mind as an emergency remedy to be resorted to in desperate cases of local or general toxemia.

Urotropin should also be studied more carefully in its relation to chemotherapy. Crowe[34] has demonstrated its lethal action on B. typhosus and B. pyocyaneus. He has also tested its sterilizing power on the body fluids by withdrawing cerebrospinal fluid through a lumbar puncture and making streptococcus cultures before and after administering the drug. He thus succeeded in reducing the bacteria from 30,000 to 500 (per plate) in the brief period of two hours. He was able to show that its maximum efficiency is exhibited in from one to five hours after its administration, although it continues to circulate in the blood for about twenty-four hours. By delicate chemical tests (Hehner) he revealed its presence in the synovial and cerebrospinal fluids, pleural effusion and blood. He found that it was eliminated in the urine, bile, pancreatic juice and saliva. Although it did not disturb the stomach it sometimes caused hematuria, which promptly disappeared when the drug was withheld. Cushing administers it to prevent infection in all injuries and operations about the head.

Barton[35] has employed urotropin in pneumococcic infection of the middle ear. He not only demonstrated its efficiency as a germicide, but also proved by accurate chemical tests that it was directly eliminated from the auditory canal about twelve hours after its ingestion. I have used urotropin with success to shorten the course of a series of cases of hypopyon keratitis, in doses of from 5 to 10 grains, three times a day. Dinkelspiel[36] has recently reported the successful administration of 40 to 80 grains daily in cases of sympathetic ophthalmitis and iridocyclitis with hypopyon. It is evident that the formalin content of this drug has a more marked sterilizing effect on the body fluids than formalin has when administered alone.

We should not overlook the fact that quinin is a most efficient therapeutic agent both from the standpoint of metabolism and of chemotherapy. It fulfills all the requirements

of the latter by being lethal to the plasmodium malaria, by neutralizing certain toxic agents in the blood and lymph stream and by stimulating fresh secretions, probably through its bitter principle. At the Wills Hospital it has long been combined with turpentine in what has been termed *"McClure's Mixture."* I have seen this combination act most efficiently in clearing up the sluggish circulation of chronic iritis and iridochorioiditis, and in relieving at least one notable case of sympathetic ophthalmitis when every other therapy had failed.

While searching for an effective chemotherapy we should not forget that the emunctories must be kept active. Elimination may be encouraged through the kidneys or by diaphoresis through the skin. Vapor baths, alone, were most efficient in bringing relief to a marked case of papilledema from la grippe, while injections of pilocarpin were successful in a case of optic neuritis following measles.

The treatment of gastro-intestinal toxemia requires (1) correction of all dietetic errors, (2) strong digestive principles to fully digest the food and promote its assimilation, (3) intestinal antiseptics to allay fermentation, such as thymol (Henry), resorcin, bismuth salicylate or potassium permanganate, and (4) thorough emptying of the intestines by vegetable and saline cathartics, or by intracolonic lavage.

Hypodermoclysis should be resorted to whenever there is impending danger of post-diphtheritic paralysis, in order to dilute the toxic fluids and thereby weaken their corrosive action. The same principle is involved in the injection of fluids into the sheath of a painful nerve. It is not so much the character or composition of the fluid injected, but the fact that it dilutes the chemically irritating fluid in the nerve sheath and thus relieves the pain.

In conclusion, the chemistry of metabolism demands for its scientific elucidation a skilled biochemist who should have a higher special training even than the bacteriologist. The chemical pathologist must work hand in hand with the internist or much of his effort will be wasted for lack of correlated clinical knowledge. He should have infinite patience in utilizing the minute quantities of secretion that can be secured for his investigations, and must, therefore, be a microchemist. It should be his aim to work out toxin reactions that can be used for local or general tests, just as the bacteriologist

has partly succeeded in securing bacterial reactions. When he has reached this point he will be able to furnish us with chemical and antitoxin reagents which will supplement our serums and bacterins and thus provide us with a more rational method of diagnosis and treatment.

In our search for an efficient chemotherapy to restore the balance of metabolism we should always preserve our proper relation to the normal chemistry of the body fluids by utilizing the following physiologic methods:

1. Administer those chemicals which will neutralize the irritating toxins and sterilize the body fluids, thereby inhibiting chemotaxis and preventing bacterial growth.

2. Increase the systemic oxidation by removing all respiratory obstruction and improving the nasal ventilation and sinus drainage.

3. Inhibit perverted lymphatic secretions by the proper therapy.

4. Stimulate fresh lymphatic secretions by the use of lymphagogues.

5. Administer glandular extracts when the internal secretions are deficient or perverted.

6. Correct gastro-intestinal errors by dietetic, digestive, antiseptic and purgative measures.

7. Eliminate katabolic products by diaphoresis and stimulate the normal activity of the skin.

8. Encourage elimination by the kidneys.

9. Reduce high blood pressure and regulate the cardiac and peripheral circulation.

10. Employ hypodermoclysis (local or general), when the poisons are unusually virulent, in order to quickly dilute the body fluids and thus lessen the corrosive action of the concentrated toxins.

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